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Transdermal Nitroglycerin in Angina Pectoris: Efficacy of Intermittent Application

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Continuous application of transdermal nitroglycerin appears to result in tolerance to the antianginal effect. In a double-blind study the effects of continuous (24 h/day) and intermittent (16 h/day) application of transdermal nitroglycerin in a dosage of 10 mg/day were compared with the effects of placebo in 12 patients with chronic stable angina receiving treatment with beta-adrenergic blocking or calcium channel blocking agents. Exercise performance was assessed 2 to 4 hours after initial application and after 1 week of each treatment given in random order with a 3 day interval between treatments.

Exercise time to onset of angina, total exercise duration and time to 1 mm ST segment depression were all significantly increased after initial application during the continuous and intermittent treatment periods. These increases were maintained after 1 week of intermittent but not continuous treatment. Thus the benefit of initial application of transdermal nitroglycerin is maintained with intermittent treatment and a daily nitrate-free interval, whereas tolerance to antianginal effect occurs with continuous treatment.

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Transdermal nitroglycerin is currently widely used in the treatment of angina pectoris. This method of nitrate administration is convenient for patients and can provide constant serum drug levels (1). However there is increasing evidence that sustained administration of nitrates can produce tolerance (2–4). Several studies (5–9) with transdermal nitroglycerin have failed to show persisting therapeutic effect despite demonstrable benefit during the first few hours of treatment. That the therapeutic effect of transdermal nitroglycerin might be maintained using intermittent application with a daily nitrate-free interval is suggested by the long-term efficacy of short-acting nitrates. Thus, this study was designed to compare the effects of continuous and intermittent administration of transdermal nitroglycerin with placebo. The effects of treatment were evaluated with exercise testing in a group of patients with chronic stable angina but relatively severe coronary artery disease who continued to receive other antianginal medications.

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Methods

Study patients (Table 1). The study group comprised 12 men, aged 38 to 70 years (mean 58), with chronic stable angina pectoris, who had a positive treadmill exercise test for ischemia and whose angina was responsive to sublingual nitroglycerin. Six patients had had previous myocardial infarction. Eleven patients had undergone coronary angiography; 10 had significant three vessel disease and 1 had two vessel disease. Eleven patients were taking a beta-adrenergic blocking agent; five of these were also taking a calcium channel blocker, and one patient was taking a calcium channel blocker only. Patients with myocardial infarction within the previous 3 months, unstable angina, significant hypertension (systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg), valvular heart disease, heart failure or electrocardiographic (ECG) abnormalities precluding interpretation of exercise-induced ST segment changes were not considered for the study.

Study design. The study period consisted of a control week followed by three treatment periods, each of 1 week's duration, chosen in random order in a Latin square design. The treatment periods were separated by a washout period of 3 days before crossover. During the treatment periods, active and placebo transdermal systems were applied in a double-blind fashion such that continuous, intermittent or placebo treatment was provided. Patients applied a transdermal system to the anterior chest wall on first awakening

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Table 1. Clinical Data in 12 Patients

Patient No.	Age (yr)	Previous MI	Duration of Angina (yr)	Coronary Angiography	Treatment	
					Beta-Blocker	Calcium Channel Blocker
1	51	–	1	Three VD	+	–
2	60	–	5.5	Three VD	+	+
3	63	–	0.5	Three VD	+	–
4	60	–	0.8	Two VD	+	+
5	55	–	16	Three VD	+	+
6	38	+	2.5	Three VD	+	+
7	67	+	14	Three VD	+	–
8	58	+	4	Three VD	–	+
9	52	–	0.5	Three VD	+	–
10	70	+	2	Three VD	+	+
11	57	+	11	Three VD	+	–
12	63	+	18	—	+	–

MI = myocardial infarction; VD = vessel disease; – = no; + = yes.

in the morning and replaced it each night on retiring. An active dose of 10 mg/day (20 cm^2) (Nitroderm TTS Ciba) was given to all patients. If intolerable side effects occurred, the dose was halved for the remainder of the study. During the continuous treatment period, the active system was replaced with a similar system on retiring, thus administering transdermal nitroglycerin 24 hours each day. For intermittent treatment, the active system was replaced with an identical placebo system allowing a nitrate-free interval of approximately 8 hours overnight. For placebo treatment, placebo systems were applied during the day and night. All long-acting nitrates were discontinued before entry into the study, but other medications including beta-blockers and calcium channel blockers were continued unchanged throughout the study period.

Exercise testing. A bicycle exercise protocol was devised for each patient during preliminary assessment, at which time the patient was familiarized with the exercise procedure (10). A Bosch bicycle ergometric system (ERG 551) was used with an integrated programmer and a speed-independent constant loading system. An initial load of 40 W was applied with 20 W increments at 3 minute intervals. The initial load was adjusted to 20 or 60 W if necessary to ensure the onset of angina within 3 to 9 minutes of the start of exercise. Patients developing angina within 3 minutes at the lowest starting load (20 W) and those asymptomatic after 9 minutes with the highest starting load (60 W) were excluded.

For each subsequent exercise assessment during the control and treatment periods, duplicate tests were performed separated by a rest interval of 30 minutes. For inclusion in the trial, <15% variation in the time to symptomatic end points was required for the control tests. If later during the treatment phase there was >15% variation in duplicate tests, a third test was undertaken after a further rest period. End points were then averaged for two or three tests.

Exercise tests were performed at the end of the control week and at the beginning (day 1) and end (day 8) of the three treatment weeks between 2 and 4 hours after morning application of the transdermal system. A 12 lead ECG monitoring system was used with recording of leads II, III, avF, V_2, V_4, and V_6 at 15 second intervals. Blood pressure was measured at 3 minute intervals and at onset of angina using an automated system.

Exercise end points were: 1) time to onset of angina; 2) total exercise duration (the stage at which the patient would normally cease exertion); 3) time to 1 mm ST segment depression (taken from the lead showing earliest ST segment depression); and 4) heart rate-systolic blood pressure product at onset of angina.

Table 2. Exercise Testing Results in 11 Patients

	Control	Placebo		Continuous		Intermittent	
		Initial	1 Week	Initial	1 Week	Initial	1 Week
Time to onset (s)	348 ± 80	374 ± 108	365 ± 103	446 ± 146*	362 ± 101	459 ± 125*	429 ± 128†
Exercise duration (s)	410 ± 76	442 ± 105	420 ± 99	491 ± 130*	419 ± 101	515 ± 122*	489 ± 115†
Time to 1 mm ST depression (s)	332 ± 66	350 ± 109	331 ± 83	437 ± 120*	345 ± 98	465 ± 114†	426 ± 95‡
Rate-pressure product (beats/min × mm Hg/100)	136 ± 33	131 ± 27	138 ± 37	145 ± 26*	137 ± 29	151 ± 33*	147 ± 43

Values are mean ± SD; *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$ versus placebo.

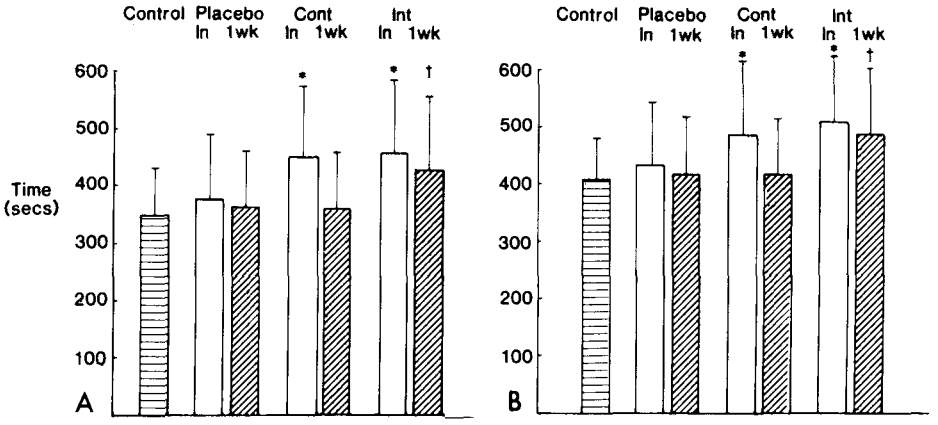

Figure 1. Time to onset of angina (**A**) and total exercise duration (**B**) for control, placebo, continuous (Cont) and intermittent (Int) transdermal nitroglycerin treatment periods in 11 patients. Exercise results were similar for control and placebo periods but were significantly increased after initial application (In) of both continuous and intermittent treatments and after 1 week (1wk) of intermittent treatment. Values are mean values ± SD; * $p < 0.05$, † $p < 0.01$ versus placebo.

A diary record of angina frequency and sublingual nitroglycerin consumption was kept by all patients during the control and treatment periods.

Statistical analysis. Group data were compared using the paired Student's *t* test. A probability (p) value of <0.05 was considered statistically significant.

Results

Eleven patients completed the study, one being withdrawn because of an intercurrent illness during treatment. No period or order effect was evident on data analysis. Group data from the control and treatment periods are summarized in Table 2 and Figure 1. Total exercise duration for individual patients is shown in Table 3.

Exercise test results. Exercise results were similar for control and placebo treatment periods. After initial transdermal system application on day 1 of the continuous and intermittent treatment periods, time to onset of angina, total exercise duration, time to 1 mm ST depression and rate-pressure product at onset of angina were all significantly increased compared with values during administration of placebo. However, after 1 week of continuous treatment there was no significant difference compared with placebo. In contrast, time to onset of angina, exercise duration and time to ST depression remained significantly increased after 1 week of intermittent treatment.

Angina frequency. There was no significant difference in angina frequency or sublingual nitroglycerin consumption between the continuous or the intermittent treatment period and the placebo period.

Adverse effects. Three patients experienced severe headache during treatment but were able to complete the study after reduction of transdermal nitroglycerin dosage to 5 mg/day. Another patient experienced tolerable mild headache during treatment and dosage alteration was not required. No significant local skin reactions occurred.

Discussion

In this study we have shown that the antianginal effect of transdermal nitroglycerin demonstrable after initial application is maintained with intermittent application and a

Table 3. Total Exercise Duration (s) for 11 Individual Patients

Patient No.	Control	Placebo		Continuous		Intermittent	
		Initial	1 Week	Initial	1 Week	Initial	1 Week
1	475	447	468	582	442	592	595
2	528	599	594	603	525	601	623
3	361	445	432	506	452	376	547
4	487	603	528	628	505	663	614
5	442	340	348	341	340	491	388
6	357	392	442	598	433	526	355
7	403	398	340	333	306	424	403
8	408	394	471	562	486	635	608
9	453	578	437	596	554	654	534
10	309	312	298	309	261	363	378
11	481	—	—	Withdrawn		—	—
12	286	356	265	341	280	343	340
Mean (± SD)	410 ± 76	442 ± 105	420 ± 99	491 ± 130	419 ± 101	515 ± 122	489 ± 115

daily nitrate-free interval, whereas tolerance occurs with continuous application.

Limitations of the study. The patients studied had relatively severe coronary artery disease and it was not considered appropriate to withhold concomitant medication in this group during the study period. Although such concomitant medication, and calcium channel blockers in particular, might have influenced the response to treatment, results in the six patients taking a calcium channel blocker were similar to those in the other five patients. The limitations of exercise testing in assessing patients with angina pectoris are widely acknowledged. However, patients were carefully selected for the study, the exercise protocol was individualized and repeated exercise testing was applied to reduce variability with serial evaluation. With this method of assessment, a treatment effect was demonstrated after initial application and this effect was maintained with intermittent but not with continuous treatment. Nevertheless, exercise testing at a single time interval after treatment application does not allow one to conclude that, after intermittent treatment, exercise tolerance is comparable throughout the day. Time-dependent depression of antianginal effect may have been evident if testing was performed at different time points after application, and this remains a limitation of our study. The slight variability in the timing of exercise testing (between 2 and 4 hours after treatment application) is a potentially confounding factor. However, the time interval did not vary for individual patients and there was no relation between the duration of the interval to testing and the amount of change between the beginning and end of active treatment periods among patients.

Tolerance to transdermal nitroglycerin. Several controlled studies have demonstrated rapid attenuation of the therapeutic effect of transdermal nitroglycerin. Reichek et al. (5) titrated nitroglycerin dosage to lower sitting blood pressure by 10 mm Hg or to increase heart rate by 10 beats/min. With a mean dose of 9.4 mg/day, there was no significant improvement over placebo in exercise performance at 4 or 24 hours. However, in a second limb of the same study, maximal tolerated doses (mean dose 25 mg/day) improved exercise tolerance at 4 and 8 hours but not at 24 hours. Response to sublingual nitroglycerin was maintained, suggesting that tolerance was not complete and could be overcome by an increase in plasma nitroglycerin levels. Parker and Fung (6), using doses of 5 to 15 mg/day, showed improvement in exercise time 4 hours after application but no benefit after 24 hours. With continuous therapy for 1 to 2 weeks at a dose of 10 to 15 mg/day, there was no advantage over placebo at either 4 or 24 hours after reapplication. Other similar studies (8,9) have demonstrated lack of effect after sustained therapy at doses up to 20 mg/24 h.

Conflicting data come from the study of Thompson (11) in which a transdermal nitroglycerin dose of 10 to 20 mg/day significantly improved exercise performance at 2 and 26 hours after application. This result was achieved even though some patients had a 10 day titration period before definitive exercise testing. Scardi et al. (12) also recorded a positive experience showing that a dose of 10 or 20 mg/day improved exercise capacity at 4 and 24 hours after application. However, considerable attenuation of therapeutic effect had occurred by 24 hours.

Dosage and mechanisms of tolerance. Although we used a relatively low, fixed nitroglycerin dose of 10 mg/day, it was not tolerated in three cases. It is possible that continuous treatment may be more effective with higher doses. Parker and Fung (6) assessed the effect of a high dose of 45 mg/day. Exercise time was prolonged at 2 and 4 hours compared with placebo and, although still significantly prolonged at 24 hours, it was clearly attenuated. Although the mechanism of tolerance is not fully understood, it may relate to depletion of sulfhydryl groups that mediate relaxation of smooth muscle by nitroglycerin (13,14). Thus, higher dosage may not necessarily overcome tolerance and, indeed, higher dosage for more prolonged periods might theoretically produce more complete tolerance requiring a longer nitrate-free interval to reestablish therapeutic effect. Although repletion of sulfhydryl groups may prevent tolerance (15), the alternative provision of a nitrate-free interval appears more practicable.

Implications. Although we have shown that a nitrate-free interval of approximately 8 hours allows maintenance of therapeutic effect of transdermal nitroglycerin, further studies are required to more accurately define the minimal nitrate-free interval required. Most patients require antianginal effect during the active waking hours, and overnight removal and morning reapplication of transdermal systems is convenient. However, it will be necessary to consider the optimal timing of the nitrate-free interval during the 24 hour period and, possibly, in some cases the necessity of providing alternative protection from ischemia during this time.

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